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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/066,498	01/30/2002	Jong-Gu Park	57354-00002	5213

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EXAMINER	
SCHULTZ, JAMES	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 12/05/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/066,498	PARK ET AL.	
	Examiner	Art Unit	
	J. Douglas Schultz	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 September 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-47* is/are pending in the application.

4a) Of the above claim(s) *12-21,24-29,40 and 43-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22,23,30-39,41,42,46 and 47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Application/Amendment/Claims

1. Applicant's response filed September 3, 2003 has been considered. Rejections and/or objections not reiterated from the previous office action mailed June 19, 2003 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments

3. Claims 30, 31, 33-37, and 39 are rejected under 35 U.S.C. 102(b) as being anticipated by Hellmann et al. (Virology. 1985 143:23-34), and is repeated for the reasons of record set forth in the Office action mailed June 16, 2003. Although applicants have canceled the original claims necessitating this rejection, the rejection is maintained against the newly recited claims above because the instant subject matter is considered analogous if not identical to the originally rejected claims.

Applicants have traversed this rejection by asserting that Hellmann fails to disclose or suggest mixing the M13 molecule with a transfection effective composition such as liposome, because Hellmann's assays with the M13 molecule is conducted entirely in a cell-free system. This is not considered convincing, because the "liposome" example is but one example of the broad number of "transfection effective carriers" that are actually claimed by applicants. In fact, also contained within such broad language is any number of solutions in which Hellman indicates the M13/antisense compound was stored or manipulated in. For example, Hellman

states that their M13/antisense compound was grown in E. coli cells, which necessarily indicates that the compound was transfected and was thus in a transfection effective carrier. Accordingly, this newly added limitation does not free the claim from the teachings of Hellman et al. Furthermore, because it is not clearly established what the lower length limit of the claim language reciting "at least about 3000 nucleotides" is, and because Hellman teaches the use of M13 vectors which are known in the art to be greater than 3000 nucleotides, the compound of Hellman is considered to fall within the scope of a reasonably broad interpretation of such "about" language. Thus, Hellman is still considered to possess all the limitations of the compound of the claims above, and the rejection is maintained.

4. Claims 23 and 42 are rejected under 35 U.S.C. 102(b) as being anticipated by Moon et al., and is repeated for the reasons of record set forth in the Office action mailed June 16, 2003. Although applicants have canceled the original claims necessitating this rejection, the rejection is maintained against the newly recited claims above because the instant subject matter is considered analogous if not identical to the originally rejected claims.

Applicants have traversed the instant rejection, on the grounds that Moon fails to disclose or suggest a large circular single-stranded nucleic acid molecule, which is at least about 3,000 nucleotides long and/or comprises a recombinant bacteriophage or phagemid genome, wherein the molecule further comprises at least one target-specific antisense region, wherein the large circular single-stranded nucleic acid molecule is effective for reducing the expression of the gene; and a transfection effective carrier thereof.

This is not considered convincing, because the Moon teaches the limitations of the claims listed above. Regarding the assertions that Moon et al. does not teach a large circular single-stranded nucleic acid molecule that is at least about 3,000 nucleotides long or comprises a recombinant bacteriophage or phagemid genome, it is pointed out that these limitations are not found in the claims. Furthermore, at page 4650 at the top of the right hand column, Moon teaches that their molecule comprises several target-specific antisense region, six such sequences to be exact. Moon also teaches in figure 6 that such molecules are effective at reducing the expression of the gene target, and that said molecules were administered to cells in culture using liposomes, which qualify as a transfection effective agent.

Regarding the limitation that the instantly claimed molecules are specific for a plurality of target genes, such language does not specify if said plurality of target genes need to be different from one another. Moon indicates that many c-myb molecules were inhibited, and that thus a plurality of targets were inhibited; thus, Moon et al. is considered to teach the limitations of the instant claims listed above.

5. Claims 23, 30-32, and 42 are rejected under 35 U.S.C. 102(b) as being anticipated by LaPlante et al. (Biochem J. 2000. 348:189-199), and is repeated for the reasons of record set forth in the Office action mailed June 16, 2003. Although applicants have canceled the original claims necessitating this rejection, the rejection is maintained against the newly recited claims above because the instant subject matter is considered analogous if not identical to the originally rejected claims.

Applicants have traversed the instant rejection, on the grounds that Laplante fails to disclose or suggest a large circular single-stranded nucleic acid molecule, which is at least about 3,000 nucleotides long and/or comprises a recombinant bacteriophage or phagemid genome, wherein the molecule further comprises at least one target-specific antisense region, wherein the large circular single-stranded nucleic acid molecule is effective for reducing the expression of the gene; and a transfection effective carrier thereof.

This is not considered convincing. As a matter of record, the comprising language of the above claims, despite applicants' recitation that the nucleic acid is single stranded, is considered open language that would also include any double stranded nucleic acid as well, since all double stranded nucleic acids comprise single stranded nucleic acids. When viewed in this light, applicants' arguments are not sufficient to free the claims from the prior art. To be specific, LaPlante teaches a large circular nucleic acid molecule comprising a single strand which is at least about 3,000 nucleotides long. The above claims do not recite a recombinant bacteriophage or phagemid genome, so arguments drawn thereto are not relevant in this rejection. LaPlante teaches said molecule further comprising a target-specific antisense region that is complementary to an entire gene and which is effective for reducing the expression of the gene, and a transfection effective carrier thereof.

6. Claims 22, 23, 46 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hellman et al., in view of Hu et al. (U.S. Patent Number 6,107,062), and is repeated for the same reasons of record as set forth in the Office action mailed June 16, 2003. Although applicants have canceled the original claims necessitating this rejection, the rejection is maintained against

the newly recited claims above because the instant subject matter is considered analogous if not identical to the originally rejected claims.

Applicants have traversed the instant rejection on the grounds that the instant references are not combinable with each other the purposes for which each reference uses either the single-stranded or double-stranded form of either the phage or the plasmid vector are different, and that therefore, a person of ordinary skill in the art reviewing the Hellmann reference would not be motivated to consider using a plasmid DNA to solve the hybridization problem discussed in the Hellmann reference. Applicants also argue that a person reviewing Hu would not be motivated to consider the single-stranded M13 vector construct of Hellmann, and assert that there is no motivation found in either reference to combine these two references.

This is not considered convincing, because applicants reason for the lack of combinability, namely that a person reviewing the Hellmann reference would not be motivated to use the construct of Hu to solve a hybridization problem in Hellmann, does not address the motivation set forth in the previous rejection. Since Hellmann teaches that circular nucleic acids are more resistant to degradation, and since Hu at col. 3 teaches that resistance to degradation is desired because it serves to increase the concentration of the therapeutic nucleic acid in the cell, a clear motivation to combine has been set forth. Furthermore, since Hu teaches using multiple antisense regions on their molecule, and since Hellmann targeted two regions of their target, one of skill would have been motivated to combine the multiple region targeting using a single vector as in Hu with the enhanced nuclease resistance of Hellmann. Therefore, applicants assertion that an alleged problem of one reference (i.e. Hellmann) is not solved by the other reference (i.e. Hu)

is not convincing since the alleged problem would not prevent their combination, and when there are other reasons for their combination.

Applicants further argue that because Hu discloses expressing antisense RNA sequence from a plasmid inhibit native target RNA, that a person of ordinary skill in the art would not be motivated to look toward using single-stranded M13 to express target specific RNA sequence, because the M13 construct in Hellmann is not used for expressing any target specific antisense RNA sequence from its M13 vector. That the references are different is not disputed. However it fails to be seen how such a difference prevents their combination. Simply because applicant is able to describe a hypothetical mechanism by which the teachings would not yield a useful product would not lead one of ordinary skill to the conclusion that such references are prevented from being combined. They are combinable because Hu set forth the concept of using one vector to deliver single stranded antisense molecules that possess the ability to target multiple target regions, and because Hu further discusses the problem of nuclease degradation. Hellmann offers a solution to that problem. The fact that the vector of Hellmann is not used to express antisense oligos does not appear relevant. The rejection is thus maintained.

Claim Objections

7. Claims 46 and 47 are objected to because of the following informalities: the term "liposome" in both claims is lacking the article "a". Appropriate correction is required.

Claim Rejections - 35 USC § 112

8. Claims 22 and 34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 22 recites the limitation "said genes" when there is no previous reference in the claim to said genes. Thus, there is insufficient antecedent basis for this limitation in the claim.

b. Claim 34 recites the limitation "said bacteriophage or phagemid" in claim 30. There is insufficient antecedent basis for this limitation in claim 30.

Claim Rejections - 35 USC § 103

9. Claims 38, 46, and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hellman et al., in view of Moon et al. (above), and LaPlante et al. (above). Although applicants have canceled the original claims necessitating this rejection, the rejection is maintained against the newly recited claims above because the instant subject matter is considered analogous if not identical to the originally rejected claims.

The invention of the above claims is drawn to a large circular nucleic acid containing an antisense region that is substantially complementary to an entire gene sequence, or wherein said composition comprises a liposome.

Hellman et al. is as taught above, but specifically teach a large circular nucleic acid comprising a target specific antisense region that specifically binds to a portion of RNA expressed from a gene. Hellman does not teach the use of a full length antisense transcript or the use of such compounds in combination with a liposome.

Moon et al. teach a circular nucleic acid comprising a target specific antisense region that specifically binds to a portion of RNA expressed from a gene, wherein said antisense molecule is administered with a liposome.

LaPlante et al. teaches a large circular nucleic acid molecule comprising a target specific antisense region that is fully complementary to an entire gene sequence.

It would have been obvious to use the large circular nucleic acids as taught by Hellman et al. and insert a full length antisense nucleic acid transcript directed against the full target as disclosed by LaPlante et al. Furthermore, it would have been obvious to one of ordinary skill in the art to use liposomes to assist in transfecting cells with such nucleic acids. One would have been motivated to use the full length antisense transcript because LaPlante et al. teach that such transcripts are successfully used to inhibit a target, and that they are commonly used in combination with large plasmid vectors. One of ordinary skill would thus be motivated to use the full length transcript in place of the antisense region of Hellmann. Moreover, since Moon et al. teach the use of circular nucleic acid inhibitors similar to those of Hellmann, and since Moon state at the 2nd to last paragraph on page 4652 that a meaningful level of oligo uptake should be consistently obtainable when carried into cells by liposomes, regardless of the size of the oligo, one would be motivated to combine the nucleic acids of either Moon or Hellmann with liposomes as taught by Moon. One of ordinary skill in the art would have had a reasonable

expectation of success, because Moon clearly states that "the relatively large size of RiAS oligos should not pose a problem for efficient cellular uptake". Therefore in the absence of evidence to the contrary, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Double Patenting

10. Applicant is advised that should claim 23 be found allowable, claim 42 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz whose telephone number is 703-308-9355. The examiner can normally be reached on 8:00-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone number for the organization where this application or proceeding is assigned is 703-305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

James Douglas Schultz, PhD